DATA EVALUATION RECORD

BAS 670H

Study Type: §82-1b, 90-Day Oral Toxicity Study in Dogs

Work Assignment No. 1-01-11 G (MRID 45902205)

Prepared for
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DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity in Dogs (diet); OPPTS 870.3150; OECD 409.

PC CODE: 123009 **DP BARCODE:** D292904

TEST MATERIAL (PURITY): BAS 670H (95.2-95.8% a.i.)

SYNONYMS: [3-(4-5-Dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methyl-phenyl]-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-methanone

CITATION: Kaspers, U., K. Deckardt, W. Kaufmann, et al. (2002) BAS 670H - Subchronic oral toxicity study in Beagle dogs: Administration in the diet for 3 months. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Rhein, Germany. Laboratory Project ID: 31D0124/98110, May 23, 2002. MRID 45902205. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products, P.O. Box 13528, Research Triangle Park, NC

EXECUTIVE SUMMARY - In a subchronic oral toxicity study (MRID 45902205), BAS 670H (95.2-95.8% a.i., Batch/Lot #s: N17 & N26) was administered to Beagle dogs (5/sex/dose) in a diet at doses of 0, 3000, 9000, or 25,000 ppm (equivalent to 0/0, 182/205, 535/624, or 1511/1712 mg/kg/day [M/F]) for up to 90 days.

No adverse treatment-related effects were observed on mortality, clinical signs, food consumption, hematology, clinical chemistry, gross or histopathology parameters.

Decreased body weight gains were observed in males at 25,000 ppm throughout treatment with the terminal body weight decreased by 10% ($p \leq 0.05$). Food efficiency was decreased by 28-338% compared to controls in the 25000 ppm males throughout the study. No significant differences in body weights were observed at any dose in females; decreased body weight gains were noted at all doses; however, no dose response was seen.

Urinalysis showed increased ketone level in the urine of all treated animals of both sexes. This finding may be a false positive due to excretion of p-hydroxyphenylpyruvic acid (a keto-acid) which interferes with the reagent of the test strip. Increased incidence of crystal (identified as magnesium complex of the parent compound) was seen in urine sediments of 25000 ppm males.

Absolute brain weight was decreased ($p \leq 0.01$) by 15-16% in the ≥9000 ppm females; however, the relative brain weight were comparable in all doses. In addition, as there was no corroborative histopathological evidence in the brains of these animals, this finding is of equivocal toxicological importance. Histopathology revealed inflammation in the urinary bladder of two male dogs at the 25000 ppm. All other histopathological findings were either incidentally as single case or were equally distributed over the dose groups.

The NOAEL for males is 9000 ppm (equivalent to 535 mg/kg/day), and the LOAEL is 25,000 ppm (equivalent to 1511 mg/kg/day) based on decreased body weight gain, impaired food efficiency, and inflammation of the urinary bladder. The NOAEL for females is 25000 ppm (equivalent to 1712 mg/kg/day), the LOAEL for females is not established.

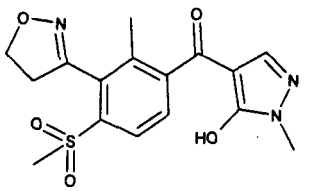
This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3150; OECD 409) for a 90-day oral toxicity study in the dog.

COMPLIANCE - Signed and dated GLP, Data Confidentiality, Quality Assurance, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: BAS 670H

Description:	Beige solid
Batch/Lot #s:	N17 & 26
Purity (w/w):	95.2-95.8% a.i.
Stability of compound:	The test material was stable in the diet for up to 49 days at room temperature or in the dietary paste for up to 24 hours at room temperature.
CAS #:	210631-68-8
Structure:	

2. Vehicle - Dietary paste (350 g food with 350 mL water daily)

3. Test animals

Species:	Dog
Strain:	Beagle
Age/weight at initiation of treatment:	Approximately 5-7 months old; 9.5-13.6 kg males, 7.9-13.0 kg females
Source:	BASF
Housing:	Individually in 5.4 m^2 indoor/outdoor kennels
Diet:	Dog Maintenance Laboratory Diet (Provimi Kliba SA, Kaiseraugst, Switzerland), 350 g of food (with 350 mL of water) for 2 hours each day, except for fasting in metabolism cage
Water:	Tap water, *ad libitum*; except when in metabolism cage, 500 mL
Environmental conditions	
Temperature:	Not reported. Note: The report stated that the animal room were ventilated by a forced ventilation system, with additional heating of the air supply in winter.
Humidity:	Not reported
Air changes:	Not reported.
Photoperiod:	Natural day/night rhythm with artificial light as required during working hours
Acclimation period:	7 days

B. STUDY DESIGN

1. In life dates - Start: 11/09/99 End: 02/15/00

2. Animal assignment - The dogs were randomly assigned, stratified by body weight, to the test groups shown in Table 1.

Table 1. Study design [a]

Test Group	Dose (ppm)	Achieved Intake (mg/kg/day, M/F)	# of Animals (M/F)
Control	0	0/0	5/5
Low	3000	182/205	5/5
Mid	9000	535/624	5/5
High	25,000	1511/1712	5/5

a Data were obtained from the study report, pages 21 and 45.

3. **Dose selection rationale** - No dose rationale was provided.

4. **Treatment preparation, administration, and analysis** - For each dose level, the appropriate amount of test substance was mixed with a small amount of diet to form a premix. The premix was further diluted with diet to achieve the proper dose levels. Test diets were prepared approximately every two weeks and then stored at room temperature. The control animals received the standard diet alone. All animals were fed daily using 350 g of ground diet mixed with 350 mL of water (to form a paste). Homogeneity was confirmed by analyses of three samples each taken from the 3000 and 25,000 ppm diets on Days -5 (initial dietary formulation with batch#: N17), 37 (when the new batch#: N26 was used), and 66 (the final dietary formulation with batch#: N26. Stability of the test substance in the diet was confirmed in a 5000 ppm diet for up to 49 days at room temperature, and in the dietary paste for up to 24 hours at room temperature. Concentration analyses were reported for each dietary dose level on Days -5, 37, and 66.

Results - **Homogeneity (range as % of nominal):** 103.8-110.7%

Stability (range as % initial):

Up to 49 days in the diet at room temperature: 99.3-105.9%
Up to 24 hours in dietary paste at room temperature: 96.4-98.5%

Concentration:

Dose (ppm)	% Nominal
3000	103.8-108.7
9000	106.3-106.7
25,000	108.0-110.7

The analytical data indicated that the mixing procedure was adequate and the variation between nominal and actual dosage to the animals was acceptable.

6. **Statistics** - The following statistical procedures were employed:

Parameter	Statistical Test
Body weight	Parametric one-way analysis using the F-test (ANOVA) followed by Dunnett's test, if necessary
Hematology and clinical chemistry parameters (except differential blood count)	Non-parametric one-way analysis using the Kruskal-Wallis test followed by the Mann-Whitney U-test for equal medians, if necessary
Urinalysis parameters (except color, volume, turbidity, and specific gravity)	Fisher's exact test
Organ weights	Non-parametric one-way analysis using Kruskal-Wallis test followed by the Wilcoxon test, if necessary

Significance was defined at $p \leq 0.05$. In general, the statistical methods were considered appropriate. However, it was not stated whether normal distribution or homogeneity of variances were determined for any of the data. These assumptions should be verified before proceeding with parametric analyses.

C. METHODS

1. Observations

a. Cage-side observations - Animals were inspected at least once daily for clinical signs of toxicity. All animals were checked for moribundity and mortality twice daily on weekdays and once daily on weekends and holidays.

b. Clinical examinations - Detailed physical examinations including, but not limited to, the following were performed prior to the start of administration and weekly thereafter: general state, body position and body posture, activity and behavior, skin and fur, mucosal membranes, eyes and nose, reflexes, respiration, visible swellings and masses, and urine and stool.

c. Neurological evaluations - Neurological evaluations were not performed; however, acute (MRID 45902303) and subchronic (MRID 45902201) neurotoxicity studies in the rat were reviewed concurrently.

2. Body weight - All animals were weighed prior to the study, at initiation of treatment, weekly throughout the study, and at termination. Cumulative body weight gain was reported weekly.

3. Food consumption, food efficiency, and compound intake - Food consumption (g/animal/day) was recorded daily for each dog. Test substance intake (mg/kg bw/day) was calculated for each animal at the same intervals as body weight measurements based on

individual body weight and food consumption values and the nominal dose. Food efficiency was calculated weekly based on body weight and food consumption values.

4. Ophthalmoscopic examination - Ophthalmoscopic examinations were conducted on all dogs prior to initiation (Day -11) and prior to termination (Day 91) of the study.

5. Hematology and clinical chemistry - Blood samples for hematology and clinical chemistry analyses were collected from all animals prior to initiation of treatment (Days -4/-1 [M/F]) and on Days 41-42 and 90-91. Animals were fasted overnight (16-20 hours) prior to blood collection. The following CHECKED (X) parameters were examined. Additionally, differential blood smears and reticulocyte counts were prepared, but were not evaluated.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc. (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*		Reticulocyte count
	Blood clotting measurements*		
X	(Activated partial thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150

b. Clinical chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
X	Magnesium	X	Urea nitrogen*
X	Phosphorus*	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	ENZYMES	X	Total bilirubin*
X	Alkaline phosphatase (ALK)*	X	Total protein*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine amino-transferase (also SGPT)*		
X	Aspartate amino-transferase (also SGOT)*		
	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150

6. Urinalysis - Urine samples were collected overnight in metabolism cages (animals were fasted but received 500 mL of water) from all animals prior to initiation of treatment (Days -6/-5 [M/F]) and on Days 43/44 and 86/87. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity*	X	Bilirubin
X	pH*	X	Occult blood*
X	Sediment (microscopic)		Nitrites
X	Protein*	X	Urobilinogen
X	Turbidity		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150

7. Sacrifice and pathology - At study termination, all animals were sacrificed via exsanguination under anesthesia, weighed, and subjected to a gross pathological examination. The following CHECKED (X) tissues were collected and fixed in 4% neutral buffered formaldehyde. Additionally, the (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta, thoracic*	XX	Brain*+
X	Salivary glands*	X	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen*+	X	Eyes (with optic nerves)*
X	Jejunum*	X	Thymus*+		GLANDULAR
X	Ileum*			XX	Adrenal glands*+
X	Cecum*		UROGENITAL		Lacrimal gland (with third eyelid)
X	Colon*	XX	Kidneys*+	XX	Parathyroids*+
X	Rectum*	X	Urinary bladder*	XX	Thyroid*+
XX	Liver*+	XX	Testes*+		OTHER
X	Gall bladder*+	XX	Epididymides*+	X	Bone (sternum and/or femur)
X	Pancreas*	XX	Prostate*	X	Skeletal muscle
	RESPIRATORY	XX	Ovaries*+	X	Skin*
X	Trachea*	X	Uterus*+	X	All gross lesions and masses*
X	Lungs*	X	Mammary gland*	X	Joint (femur/tibia)
X	Nasal structures*		Cervix		
X	Pharynx*	X	Oviducts		
X	Larynx*	X	Vagina		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150
\+ Organ weight required for non-rodent studies

Tissues from all animals were processed routinely, stained with hematoxylin and eosin, and were examined microscopically.

II. RESULTS

A. OBSERVATIONS

1. Clinical signs of toxicity - No adverse treatment-related clinical signs were observed at 3000 and 9000 ppm. At 25,000 ppm, light-brown discolored feces was observed in all males and females throughout the study, and red-brown discolored urine was observed in 2/5 males between Days 69-87.

2. Mortality - All animals survived to scheduled sacrifice.

B. BODY WEIGHT AND WEIGHT GAIN - In males, terminal body weights were decreased ($p \leq 0.05$) compared to control at 25000 ppm (Table 2). At 25000 ppm, cumulative body weight gains were decreased throughout treatment period. In females, no significant differences in body weights were observed at any dose. Decreased body weight gains were noted at all doses; however, no dose response was seen.

Table 2. Selected mean (±SD) body weights and body weight gains (kg) in dogs treated with BAS 670H in the diet for up to three months. [a]

Parameter	Dose (ppm)			
	0	3000	9000	25,000
Males				
Body Weight -Day 0	11.0±1.0	11.4±1.2	11.3±0.7	11.5±1.3
Body Weight -Day 7	11.2±0.9	11.4±1.2	11.3±0.8	11.5±1.2
Body Weight -Day 21	11.6±0.8	11.6±1.3	11.6±0.6	11.6±1.1
Body Weight - Day 91	12.9±0.5	12.0±2.1	12.4±0.3	11.7±0.6*(↓10)
Body Weight Gain - Days 0-7	0.2±0.2	0.0±0.1	0.0±0.1	0.0±0.1
Body Weight Gain - Days 0-21	0.6±0.3	0.2±0.3	0.3±0.2	0.1±0.2* (↓83)
Body Weight Gain - Days 0-49	1.1±0.5	0.4±0.7	0.6±0.4	0.2±0.6 (↓82)
Overall BW Gain - Days 0-91	1.9±0.9	0.6±1.2	1.1±0.5	0.2±1.0 (↓89)
Females				
Body Weight -Day 0	9.0±0.8	9.6±1.9	9.2±1.0	9.3±1.1
Body Weight -Day 7	9.2±0.9	9.8±1.8	9.4±1.0	9.4±1.0
Body Weight -Day 21	9.7±0.7	10.1±1.7	9.7±0.9	9.8±0.9
Body Weight - Day 91	11.5±0.6	11.1±1.7	10.9±0.8	11.0±0.7
Overall BW Gain - Days 0-21	0.7±0.1	0.5±0.2	0.5±0.2	0.5±0.3
Overall BW Gain - Days 0-49	1.5±0.4	1.0±0.3	1.1±0.3	1.1±0.4
Overall BW Gain - Days 0-91	2.5±0.3	1.4±0.5** (↓44)	1.7±0.5* (↓32)	1.7±0.6* (↓32)

a Data were obtained from pages 85-92 of the study report; n=5. Percent difference from controls, calculated by the reviewers, is included in parentheses.

* Significantly different from the control group at $p \leq 0.05$

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. Food consumption/Food efficiency - Food consumption was comparable to controls in males and females throughout the study. Taking into consideration that decreased body weights were observed in males of 25000 ppm group, food efficiency was sporadically decreased by 28-338% compared to controls in 25,000 ppm males throughout the study (Table 3). No significant difference was observed in females.

Table 3. Mean (±SD) food efficiency (%) in male dogs treated with BAS 670H in the diet for up to three months. [a]

Days	Dose (ppm)			
	0	3000	9000	25,000
7	9.0±7.9	0.0±5.8	0.0±5.0	0.0±5.0
49	5.7±3.7	3.3±8.8	4.1±5.8	4.1±6.5 (↓28)
70	2.4±6.8	-3.3±7.9	0.0±5.0	-5.7±6.2 (↓338)
91	0.0±4.1	1.6±3.7	-0.8±6.1	-6.1±20.9

a Data were obtained from pages 93-94 of the study report; n=5. Percent difference from controls, calculated by the reviewers, is included in parentheses.

2. Compound intake - Mean test material intake values for the overall study are reported in Table 1.

D. OPHTHALMOSCOPIC EXAMINATION - No ocular lesions were observed in any dog at the pre-treatment or pre-terminal examinations.

E. BLOOD ANALYSES

1. Hematology - No treatment-related effects on hematology parameters were observed at any dose in either sex.

2. Clinical chemistry - No adverse treatment-related effects on clinical chemistry parameters were observed at any dose in either sex. The differences ($p \leq 0.05$) noted in various parameters were considered unrelated to treatment, because they were minor and/or not dose-dependent. No serum tyrosine level was measured.

F. URINALYSIS - Increased incidence (# affected/5 vs 0/5 controls) of elevated ketone levels in the urine was noted in the males and females at ≥3000 ppm on Days 43/44 and 86/87, respectively (Table 4). Increased incidence of crystals in the sediment was noted at 25,000 ppm in the males (4 treated vs 0 controls, Day 43; and 3 treated vs 2 controls, Day 86), and in the females (5 treated vs 2 controls, Day 44; and 2 treated vs 0 controls, Day 87).

Table 4. Selected incidences (# affected) of urinalysis findings in dogs treated with BAS 670H in the diet for up to three months. [a]

Parameter [b]	Day	Dose (ppm)			
		0	3000	9000	25,000
Males					
Ketones (>5 mmol/L)	-6	0	0	0	0
	43	0	4*	4*	5**
	86	0	4*	4*	4*
Unidentified Crystals in Sediment (masses)	-6	1	0	1	2
	43	0	0	0	4*
	86	2	1	2	3
Females					
Ketones (>5 mmol/L)	-5	0	0	0	0
	44	0	4*	2	3
	87	0	5**	3	5**
Unidentified Crystals in Sediment (masses)	-5	0	0	0	1
	44	2	2	3	5
	87	0	0	2	2

a Data were obtained from pages 53-54 and 139-150 of the study report; n=5.
b Numbers in parentheses represent semi-quantitative measures of severity.
* Significantly different from the control group at $p \leq 0.05$
** Significantly different from the control group at $p \leq 0.01$

G. SACRIFICE AND PATHOLOGY

1. Organ weight - Selected organ weight data are presented in Table 5. Absolute brain weight was decreased ($p \leq 0.01$) in the ≥9000 ppm females (↓15-16%); however, the relative brain weight were comparable in all doses. Relative (to body) thyroid weights were increased in the males at 9000 (↑43%; not significant) and 25,000 ppm (↑43%; $p \leq 0.01$). All other absolute organ weights in both sexes were similar to controls.

Table 5. Selected mean (±SD) absolute (g) and relative to body (%) organ weights in dogs treated with BAS 670H in the diet for three months [a]

Parameter		Dose (ppm)			
		0	3000	9000	25,000
Males					
Terminal body weight (kg)		13.06±0.55	12.08±2.09	12.56±0.38	11.72±0.57* (↓10)
Brain -	absolute	83.386±4.747	81.642±7.783	83.720±3.611	85.284±6.442
	relative	0.638±0.022	0.686±0.087	0.667±0.036	0.728±0.047
Thyroid -	absolute	0.942±0.156	0.930±0.246	1.196±0.194	1.154±0.236
	relative	0.007±0.001	0.008±0.002	0.010±0.002 (↑43)	0.010±0.002** (↑43)
Females					
Terminal body weight (kg)		11.80±0.68	11.30±1.74	11.08±0.80	11.28±0.63
Brain -	absolute	89.134±2.661	79.270±8.723	76.086±6.285** (↓15)	74.998±6.158** (↓16)
	relative	0.757±0.036	0.709±0.093	0.691±0.089	0.667±0.069
Thyroid -	absolute	0.962±0.248	0.908±0.226	0.740±0.170	1.154±0.180
	relative	0.008±0.002	0.008±0.002	0.007±0.001	0.010±0.002

a Data were obtained from pages 151-154 of the study report; n=5. Percent difference from controls, calculated by the reviewers, is included in parentheses.

* Significantly different from the control group at $p \leq 0.05$

** Significantly different from the control group at $p \leq 0.01$

2. Gross pathology - One male dog of the 25000 ppm group showed many ulcers in the urinary bladder. This dog also showed calculus in dilated urethra of prostate. Incidence of reduced prostate size was noted in males at ≥3000 ppm (2-4 affected/5 vs 1/5 controls); however, no significant decreases in absolute or relative (to body) prostate weight were observed, and no corroborative histopathological effects were noted. Therefore, this finding was considered not to be treatment related.

3. Microscopic pathology - Two male dogs of the 25000 ppm group showed inflammation in the urinary bladder correlated to the gross lesion ulcer. All other histopathological findings (appendix I) occurred either incidentally as single case or were equally distributed over the dose groups.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS - It was concluded that the effects of the test substance were seen at 25000 ppm only. The LOAEL was 25,000 ppm based on decreased body weight gain and impaired food efficiency in the males. The NOAEL was 9000 ppm.

B. REVIEWER COMMENTS - No adverse treatment-related effects were observed on mortality, clinical signs, food consumption, hematology, clinical chemistry, or gross or histopathology parameters.

At 25,000 ppm, body weight gains were decreased (↓79-100%) in the males throughout treatment. Likewise, food efficiency was decreased by 28-338% compared to controls in the males throughout the study. Food consumption of the treated groups was comparable in both sexes throughout the study. Terminal body weight was decreased ($p \leq 0.05$) by 10% in the males.

Absolute brain weight was decreased ($p \leq 0.01$) in the ≥9000 ppm females (↓15-16%); however, as there was no corroborative histopathological evidence in the brains of these animals, this finding is of equivocal toxicological importance.

Regarding the increased incidence of elevated ketone levels in the urine noted in both sexes at ≥3000 ppm, it was stated that the mode of action of the test material is inhibition of the enzyme p-hydroxyphenylpyruvate-dioxygenase, an enzyme involved in tyrosine catabolism in animals. The inhibition of this enzyme results in increased tyrosine levels in the blood and urine and leads to an excretion of large amounts of p-hydroxyphenylpyruvic acid (a keto-acid) in the urine, which interferes with the reagent in the test strip and causes false-positive results for ketone bodies in the urine. Additionally, the crystals in the urinary sediment noted in both sexes at 25,000 ppm were determined to be a magnesium complex of the parent compound. Thus, excessive excretion of the compound was responsible for the formation of the urinary calculi. Therefore, the increased ketones and urinary calculi were considered not to be toxicologically important.

The NOAEL for males is 9000 ppm (equivalent to 535 mg/kg/day), and the LOAEL is 25,000 ppm (equivalent to 1511 mg/kg/day) based on decreased body weight gain, impaired food efficiency, and inflammation of the urinary bladder. The NOAEL for females is 25000 ppm (equivalent to 1712 mg/kg/day), the LOAEL for females is not established.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3150; OECD 409) for a 90-day oral toxicity study in the dog.

C. STUDY DEFICIENCIES - The following minor deficiencies were noted, but do not alter the conclusions of this DER:

- Blood serum sorbitol dehydrogenase was not measured.
- The heart, spleen, thymus, gall bladder, and uterus weights were not determined.

IV. Appendix: Gross and Histopathology Report

BASF Toxicology and Ecology IC- 5
PATHOLOGY REPORT 31D0124/98110
BAS 670 H: Apr/30/2001 WEKA
3-Month Feeding in Dogs acopat system

INCIDENCE OF GROSS LESIONS

Sacrifice group	F1							
Sex	M				F			
Dose group	0	1	2	3	0	1	2	3
Animals in selected Group	5	5	5	5	5	5	5	5
NAD	3	1	2	.	5	1	4	5
Stomach	.	.	.	.	.	.	.	.
- Erosion/ulcer	.	1	.	.	.	.	1	.
Colon	.	.	.	.	.	.	.	.
- Focus	.	.	.	.	.	3	.	.
Liver	.	.	.	.	.	.	.	.
- Focus	1	.	.	1	.	.	.	.
Lungs	.	.	.	.	.	.	.	.
- Discoloration	.	.	.	.	.	1	.	.
- Focus	1	1	1	.	.	.	.	.
Kidneys	.	.	.	.	.	.	.	.
- Cyst	1	.	.	.	.	.	.	.
Urinary bladder	.	.	.	.	.	.	.	.
- Ulcer	.	.	.	1	.	.	.	.
Testes	.	.	.	.	.	.	.	.
- Organ size reduced	1	.	1	1	.	.	.	.
Epididymides	.	.	.	.	.	.	.	.
- Organ size reduced	1	.	.	1	.	.	.	.
Prostate	.	.	.	.	.	.	.	.
- Calculus	.	.	.	1	.	.	.	.
- Organ size reduced	1	2	2	4	.	.	.	.
Spleen	.	.	.	.	.	.	.	.
- Focus	1	.	.	.	.	.	.	.
Brain	.	.	.	.	.	.	.	.
- Cyst	.	.	1	.	.	.	.	.
Thyroid glands	.	.	.	.	.	.	.	.
- Cyst	.	1	.	.	.	.	.	.
Pituitary gland	.	.	.	.	.	.	.	.
- Cyst	.	.	.	1	.	1	.	.

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INCIDENCE OF MICROSCOPIC FINDINGS

Sacrifice group	F1							
Sex	M				F			
Dose group	0	1	2	3	0	1	2	3
Animals in selected Group	5	5	5	5	5	5	5	5
Pharynx	5	5	5	5	5	5	5	5
Parotid glands	5	5	5	5	5	5	5	5
- Inflammatory cells	2	3	2	2	2	3	2	1
Mandibular glands	5	5	5	5	5	5	5	5
- Inflammatory cells	.	.	.	1	4	3	2	2
Esophagus	5	5	5	5	5	5	5	5
- Mononuclear cells	.	1	1	2	2	.	2	.
- Metaplasia, focal	.	.	.	.	.	.	.	1
Stomach	5	5	5	5	5	5	5	5
- Calcification, muco.	.	1	.	.	.	1	.	.
- Hyperplasia,lymph f.	.	2	.	1	.	1	1	1
Duodenum	5	5	5	5	5	5	5	5
Jejunum	5	5	5	5	5	5	5	5
Ileum	5	5	5	5	5	5	5	5
Cecum	5	5	5	5	5	5	5	5
Colon	5	5	5	5	5	5	5	5
- Erosion, focal	.	.	.	.	.	1	.	.
Rectum	5	5	5	5	5	5	5	5
- Erosion, focal	.	.	.	1	.	.	.	.
Liver	5	5	5	5	5	5	5	5
- Granuloma(s), Kupff.	5	5	3	5	4	5	5	5
- Single cell necrosis	.	1	1	1	.	.	.	.
- Hemosiderosis,Kupff.	.	1	1	.	1	4	.	3
- Focal fat storage	1	.	.	1	.	.	.	.
- Zonal fat storage	.	.	.	.	.	.	1	.
- Inflammatory cells	1	1	2	1	1	4	1	4
- Focal necrosis	1	.	.	.	.	.	.	.
- Bile duct prolifera.	.	.	.	.	1	.	.	.
Gallbladder	5	5	5	5	5	5	5	5
Pancreas	5	5	5	5	5	5	5	5
- Inflammatory cells	.	.	.	.	.	.	.	1
Nasal cavity, III	5	5	5	5	5	5	5	5
Larynx	5	5	5	5	5	5	5	5
- Inflammation, focal	.	.	1	2	.	2	.	.
Trachea	5	5	5	5	5	5	5	5
- Inflammatory cells	.	.	.	.	.	.	.	1
Lungs	5	5	5	5	5	5	5	5
- Granuloma(s)	3	3	3	3	3	3	3	3
- Pneumonia, verminous	1	2	2	1	2	3	2	1
- Hemorrhage, acute	1	.	.	.	.	.	.	.
Kidneys	5	5	5	5	5	5	5	5
- Calcification	5	5	5	5	5	5	5	5
- Nephritis, intersti.	1	.	.	.	.	.	.	.
- Pyelonephritis	.	.	.	1	.	.	.	.
- Vasculitis, capsular	1	.	.	.	.	.	.	.
- Cyst(s)	.	.	.	.	.	.	1	.

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INCIDENCE OF MICROSCOPIC FINDINGS

Sacrifice group	F1							
Sex	M				F			
Dose group	0	1	2	3	0	1	2	3
Animals in selected Group	5	5	5	5	5	5	5	5
Urinary bladder	5	5	5	5	5	5	5	5
- Inflammation	.	.	.	2	.	.	.	.
Testes	5	5	5	5	.	.	.	.
- Giant cells	5	3	1	2	.	.	.	.
Epididymides	5	5	5	5	.	.	.	.
- Oligospermia	1	1	1	.	.	.	.	.
Prostate	5	5	5	5	.	.	.	.
- Inflammation,chronic	.	.	.	1	.	.	.	.
- Reduced size	1	3	2	4	.	.	.	.
Ovaries	.	.	.	.	5	5	5	5
- Cyst(s)	.	.	.	.	1	.	.	.
Oviducts	.	.	.	.	5	5	5	5
Uterus	.	.	.	.	5	5	5	5
- Hyperplasia, glands	.	.	.	.	1	.	.	.
Vagina	.	.	.	.	5	5	5	5
Mammary gland	.	.	.	.	5	5	5	5
Heart	5	5	5	5	5	5	5	5
- Myokarditis, focal	.	.	.	1	.	.	.	.
Aorta	5	5	5	5	5	5	5	5
Bone marrow	5	5	5	5	5	5	5	5
Spleen	5	5	5	5	5	5	5	5
- Fibrosis, focal	1	.	.	.	.	.	.	.
- Hematoma, organized	1	.	.	.	.	.	.	.
Thymus	5	5	5	5	5	5	5	5
Mesenteric lymph n.	5	5	5	5	5	5	5	5
Axillary lymph nodes	5	5	5	5	5	5	5	5
Brain	5	5	5	5	5	5	5	5
- Inflammatory cells	1	.	1	.	1	.	.	.
- Glia cell reaction	2	1	3	1	4	3	2	2
- Focal calcification	.	.	1	.	2	1	.	.
- Cyst, meningeal	.	.	1	.	.	.	.	.
Cervical cord	5	5	5	5	5	5	5	5
Thoracic cord	5	5	5	5	5	5	5	5
Lumbar cord	5	5	5	5	5	5	5	5
- Focal calcification	2	1	2	.	2	3	4	2
Sciatic nerve	5	5	5	5	5	5	5	4
- Degeneration,vacuol.	.	1	.	.	.	.	.	1
Eyes with opt. nerve	5	5	5	5	5	5	5	5
Adrenal cortex	5	5	5	5	5	5	5	5
Adrenal medulla	5	5	5	5	5	5	5	5
Thyroid glands	5	5	5	5	5	5	5	5
- C-cell hyperplasia	3	3	2	4	5	2	5	3
- Thyreoiditis	.	1	1	1	.	.	1	.
- Cyst(s)	.	.	.	.	.	.	1	.
- Hypertrophy, foll.c.	.	.	1	.	.	.	.	.
- Remnants of Rathke	1	.	.	.	.	.	.	.

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INCIDENCE OF MICROSCOPIC FINDINGS

Sacrifice group	F1							
Sex	M				F			
Dose group	0	1	2	3	0	1	2	3
Animals in selected Group	5	5	5	5	5	5	5	5
Parathyroid glands	5	5	5	5	5	5	5	5
- Cyst(s)	2	4	1	.	2	.	1	.
Pituitary gland	4	5	5	5	5	5	5	5
- Cyst(s)	2	3	.	1	2	2	.	3
Sternum, with marrow	5	5	5	5	5	5	5	5
Femur with joint	5	5	5	5	5	5	5	5
Skeletal muscle	5	5	5	5	5	5	5	4
Skin	5	5	5	5	5	5	5	5
- Follicle cyst	.	1	.	.	.	.	.	.
- Folliculitis, focal	.	1	.	.	.	.	1	1

DATA FOR ENTRY INTO ISIS

Subchronic Oral Study - non-rodents (870.3150)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Endpoints	Comments
123009	45902205	subchronic	dog	3 months	oral	diet	182-1712	0/0, 182/205, 535/624, or 1511/1712 [M/F]	535 (M) 1712 (F)	1511(M)	Decr BWG and FE in males	